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1: Proc Assoc Am Physicians 1998  
Nov-Dec;110(6):559-74

## Interleukin-6-type cytokines stimulate mesenchymal progenitor differentiation toward the osteoblastic lineage.

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Cytokines that transduce their signals either through glycoprotein 130 (gp130) homodimers or gp 130/leukemia inhibitory factor (LIF) receptor beta heterodimers are potent inducers of osteoclast development in vitro as well as in vivo; and interleukin (IL)-6 has been recognized as an important pathogenic factor in diseases characterized by increased bone remodeling, such as the osteoporosis of sex steroid deficiency. Based on evidence that the same cytokines can also promote committed osteoblast differentiation and stimulate bone formation in vitro and in vivo and that mesenchymal cell differentiation toward the osteoblast lineage may be a prerequisite for osteoclastogenesis, we have investigated whether gp130 activation can affect the differentiation of uncommitted mesenchymal progenitors. Using as our model murine embryonic fibroblasts (EF), we found that IL-6 or IL-11 in combination with their soluble receptors (sIL-6R or sIL-11R) increased dose-dependently the number of alkaline phosphatase (AP)-positive cells in 3-6-day-long cultures. Moreover, EF cells maintained with IL-6/sIL-6R in the presence of ascorbic acid and beta-glycerophosphate expressed osteocalcin messenger RNA (mRNA) by 2 weeks and formed a matrix containing mineralized collagen fibers by 3 weeks. This prodifferentiation effect was specific for the osteoblastic lineage, as we found no evidence for increased differentiation of chondrocytes, adipocytes, or muscle cells. Unlike IL-6/sIL-6R, LIF, oncostatin M (OSM), and ciliary neurotrophic factor (CNTF) did not promote osteoblastic differentiation of EF-cells. This pattern of specificity was accounted for by the finding that EF cells express gp130, but not the ligand-binding subunit of the IL-6 receptor (gp80) nor the LIF receptor beta. These observations add credence to the contention that increased production of gp130-utilizing cytokines and their receptors in pathological conditions like sex steroid deficiency is indeed responsible for not only the increased osteoclastogenesis, but also the increased

osteoblastogenesis, and thereby for the increased rate of bone remodeling.

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